acids 170-180 is highly conserved between species and is a major site of phosphorylation." Maciejewski et al was cited by the Examiner "only for the teaching that substitution of serine mimics phosphorylation." The Examiner has concluded that in view of the combination of the cited references "suggestion is in the art" for "modifying other prolactin molecules in a similar manner, i.e by substitution of the major phosphorylated serine residue, in order to mimic the phosphorylation."

Applicant disagrees and respectfully traverses the rejection. There is no motivation to combine Maciejewski et al. and Walker because one of skill in the art would not believe that Maciejewski et al. teaches that "substitution of serine mimics phosphorylation."

The Examiner noted on page 4 of the Office Action that Maciejewski et al. was cited for its alleged teaching "that substitution of the major phosphorylation site in bovine prolactin mimicked the effects of phosphorylation." In support of this position, the Examiner relies on the title of Maciejewski et al. which reads "Mutation of Serine 90 to Glutamic Acid Mimics Phosphorylation of Bovine Prolactin." Applicants note that regardless of whether the title of Maciejewski et al. is in fact supported by the experimental results, it is the substitution of *serine 90* which is claimed to mimic phosphorylation of serine 90 of bovine prolactin. Maciejewski et al. states that it is their aim to "elucidate the roles of *individual* phosphorylation sites." (see page 27662, second paragraph, emphasis added) and makes no claim that their results are generally applicable to other serine residues in prolactin of any species. Further, Maciejewski et al. teach that it is the specific structural features around serine 90 that account for their results (see discussion generally), and accordingly, teach away from a conclusion that their results are applicable to other distinct serine residues.

The Examiner, and not Maciejewski et al., has suggested that based on the findings with respect to substitution of serine 90, "one can reasonably conclude that substitution of the major phosphorylation site in prolactin from another species in the manner taught by Maciejewski et al. would also lead to mimicry of the phosphorylation." However, the Examiner has not provided any teaching or suggestion that substitution of the major phosphorylation site in prolactin of another species, i.e. human prolactin, would also lead to a mimic of phosphorylated prolactin. In fact, at the time the invention was made, one of skill in the art would <u>not</u> have reached this conclusion.

Attached to the present Response is a Declaration under 37 C.F.R. § 1.131 by Dr. Ameae M. Walker, the inventor of the present application, author of the TEM reference cited by the Examiner in the Office Action and an expert in the field. In the Declaration, Dr. Walker states that at the time the invention was made, one of skill in the art would not expect an asserted ability to mimic phosphorylated prolactin by the substitution of serine 90, to be applicable to other distinct and distant serine residues in prolactin. Further, Dr. Walker specifically states that without the benefit of the present disclosure, one of skill in the art would not expect substitution of serine residues *177 or 179 in human or bovine prolactin* to produce a mimic of naturally phosphorylated prolactin.

In view of the declaration by an expert in the field, Applicants point out that at the time the invention was made, one skilled in the art would not have concluded that Maciejewski taught that substitution of the most phosphorylated serine would mimic phosphorylated prolactin. As a result, one of skill in the art would not have been motivated to combine the cited references, as the Examiner did in making the present rejection. Further, the declaration provides evidence and sound scientific reasoning in support of the notion that, without impermissible hindsight reasoning, the cited combination of references would not establish a reasonable expectation of success for the production of a mimic of phosphorylated prolactin by substituting residues 177 or 179 which are distinct from residue 90 in human or bovine prolactin. In light of these arguments, Applicants respectfully request reconsideration and withdrawal of the present rejection.

All claims pending in this application are believed to be in *prima facie* condition of allowance, and an early action to that effect is respectfully solicited. Should the Examiner find that there are any further issues outstanding, she is respectfully invited to contact the undersigned attorney at the telephone number indicated below.

Although no fees are believed to be due at this time, please charge any fees, including any fees for extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: September 20, 2002

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